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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/572,974	03/22/2006	Stacey Ann Jones	PR60397USw	4587

23347 7590 01/25/2010

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EXAMINER	
PAGONAKIS, ANNA	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
01/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/572,974	JONES ET AL.	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,6,8,10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4, 6, 8, 10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets; 1/15/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed 10/12/2009 has been received and entered into the present application.

Applicant's arguments filed 10/12/2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

The following rejections are newly presented and are necessitated by amendment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 4, 6, 8, 10 and 13-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Kliewer et al. (U.S. 2003/0203939 A1; of record) as evidenced by Albanis (Clinics in Liver disease, Vol. 5, No. 2, 2001) and Zeremski et al. (Journal of Hepatology, 43, 2004: 2-5).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Kliewer et al. teaches a method for the treatment of cholestasis liver disease and reduction and prevention of hepatic injury resulting from cholestasis via administration of a FXR ligand, including GW4064, in an amount from about 100 ug/kg to about 5 mg/kg body weight, daily (abstract, paragraph [0008] and [0045]). For example, Kliewer et al. teach administration of the compound to a mouse model, specifically Sprague-Dawly rats, which is indicative of cholestasis, wherein serum markers of alanine aminotransferase (ALT), asparate aminotransferase (AST), gamma-glutamyl transferase (GGT), total serum bilirubin and serum bile acids change (Example 1, column 8 and claim 5). Thus, while Kliewer does not explicitly teach that a mammalian subject with changes in disease markers consistent with fibrotic disease, the claimed limitation does not appear to result in a manipulative difference because as evidenced by Zeremski et al., changes in serum markers of alanine aminotransferase (ALT), asparate aminotransferase (AST), gamma-glutamyl transferase (GGT), total serum bilirubin and serum bile acids, as taught by Kliewer et al, are consistent with fibrotic diseases. Zeremski et al. teach that AST and ALT are markers of hepatic fibrosis which are used to evaluate changes in liver histology (column 3, lines 7-10). Moreover, althought Kliewer et al. do not explicitly teach a method of reducing the development of liver fibrosis in a mammalian subject, the claimed limitation does not result in a manipulative difference because as taught by Albanis (page 2), cholestasis leads to hepatic fibrosis. Thus, it would logically flow that treatment of cholestasis as taught Kliewer et al., would reduce the development of liver fibrosis. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4, 6, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanchard et al. (WO 00/37077; of record) in view of Denson et al. (Gastroenterology, 2001; 121:140-147) and as evidenced by Albanis (Clinics in Liver disease, Vol. 5, No. 2, 2001) and Zeremski et al. (Journal of Hepatology, 43, 2004: 2-5).

Blachard et al. teach the treatment of diseases or disorders that are modulated by FXR with a compound that interacts directly with FXR, the compound being GW4064 (formula (II) on page 7 and claim 20) for the treatment of diseases in a mammal in which regulation of bile acid levels are important.

Blachard et al. is silent on the reducing the development of liver fibrosis.

Denson et al. teach that cholestasis is an important clinical feature of many immunologic, viral and toxic liver diseases which result in the accumulation of bile acids within the hepatocyte and therefore contribute to liver injury. In addition, Denson et al. disclose that intracellular bile acid levels increase

result in cholestatic liver disease. Further, Denson et al. specifically discloses that FXR ligand of GW4064 is more than 1000 times as potent than other drugs in the activation of FXR.

Albanis et al. teach that cholestasis can lead to hepatic fibrosis (page 2).

Albanis et al. is silent on the use of GW4064.

Zeremski et al. teach that AST and ALT are markers of hepatic fibrosis which are used to evaluate changes in liver histology (column 3, lines 7-10).

Zeremski et al. is silent on reducing the development of liver fibrosis with administration of the elected GW4064.

One of ordinary skill in the art would have been motivated to administer the elected FXR ligand, GW4064 for the treatment of chloestasis because GW4064 is known to regulate bile acid levels which in turn will prevent the accumulation of bile acid and therefore prevent the occurrence of cholestasis. By preventing the occurrence of cholestasis one would reduce the development of liver fibrosis since cholestasis is known to lead to liver fibrosis, per Albanis et al. Specifically, Kliewer et al. teach administration of the compound to a mouse model, specifically Sprague-Dawly rats, which is indicative of cholestasis, wherein serum markers of alanine aminotransferase (ALT), asparate aminotransferase (AST), gamma-glutamyl transferase (GGT), total serum bilirubin and serum bile acids change (Example 1, column 8 and claim 5). Thus, while Kliewer does not explicitly teach that a mammalian subject with changes in disease markers consistent with fibrotic disease, the claimed limitation does not appear to result in a manipulative difference because as evidenced by Zeremski et al., changes in serum markers of alanine aminotransferase (ALT), asparate aminotransferase (AST), gamma-glutamyl transferase (GGT), total serum bilirubin and serum bile acids, as taught by Kliewer et al, are consistent with fibrotic diseases. Zeremski et al. teach that AST and ALT are markers of hepatic fibrosis which are used to evaluate changes in liver histology (column 3, lines 7-10). Moreover, althought Kliewer et al. do not explicitly teach a method of reducing the development of liver fibrosis in a mammalian subject, the claimed

limitation does not result in a manipulative difference because as taught by Albanis (page 2), cholestasis leads to hepatic fibrosis. Thus, it would logically flow that treatment of cholestasis as taught Kliewer et al., would reduce the development of liver fibrosis. It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blanchard et al. (WO 00/37077; of record) in view of Denson et al. (Gastroenterology, 2001; 121:140-147) as applied to claims 4, 6, 8 and 10 above, and further in view of Makishima et al. (Science, 284, 1999).

The combination of Blanchard et al. (WO 00/37077; of record) in view of Denson et al. (Gastroenterology, 2001; 121:140-147) is set forth supra. The combination differs by not teaching the additional concurrent use of a naturally occurring bile acid.

Makishima et al. teach that the activation of FXR receptor by the naturally occurring primary bile acid, chenodeoxycholic acid (page 1362, column 2, lines 5-8).

One of ordinary skill in the art would be motivated to additionally administer a naturally occurring bile acid such as chenodeoxycholic acid concurrently with an FXR agonist in order to allow for a greater expression of FXR receptors which in turns allows a greater amount of FXR agonists to bind to those receptors. The greater the amount of FXR agonists which are capable of binding the greater the effect.

Claim 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blanchard et al. (WO 00/37077; of record) in view of Denson et al. (Gastroenterology, 2001; 121:140-147) as applied to claims 4, 6, 8 and 10 above, and further in view of Maloney et al. (Journal of Medicinal Chemistry, 2000).

The combination of Blanchard et al. (WO 00/37077; of record) in view of Denson et al. (Gastroenterology, 2001; 121:140-147) is set forth supra. The combination differs by not teaching a dosage amount.

Maloney et al. teach an amount of 20 mg/kg of GW4064 (page 2973, column 2, paragraph 2).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to optimize determination of a dosage having the optimum therapeutic index while minimizing adverse and/or unwanted side effects is well within the level of the skilled artisan. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of Applicant's invention. Factors that would have been taken into consideration when making such a determination would have included, but not have been limited to, the age, weight, sex, diet and medical condition of the patient, severity of the disease, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage amounts that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642